IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No.:	**09/436,347**	Group Art Unit:	1643
Confirmation No.:	6491	Examiner:	A.M. Harris
Filed:	9 November 1999		
Inventor:	Christine A. WHITE *et al.*		

For: Treatment of Chronic Lymphocytic Leukemia using Anti-CD20 Antibodies (as amended)

SECOND DECLARATION OF DAVID P. SCHENKEIN, M.D. UNDER 37 C.F.R. § 1.132

1. I am Senior Vice President, Clinical Hematology/Oncology at Genentech, Inc. (licensee of the above patent application). Genentech, a licensee of patent application No. 09/436,347 ("the '347 application"), co-promotes RITUXAN® (rituximab), a therapeutic CD20 antibody, in the United States together with Biogen Idec Inc., the owner of the patent application.

2. I have previously provided a declaration in this case. As I explained in that declaration, I specialize in the field of hematologic malignancies, and was actively treating chronic lymphocytic leukemia (CLL) patients in November of 1998 when the '347 application was filed. My credentials and background are essentially as I described them in my previous declaration.

3. I have reviewed the final Office action of February 19, 2009 ("Final Action"). I have also reviewed the following patents and publications cited in the Final Action:

   - RITUXAN® (rituximab) package insert dated November, 1997;
   - U.S. Patent No. 5,843,398 ("Kaminski '398 patent") and U.S. Patent No. 6,090,365 ("Kaminski '365 patent");
   - U.S. Patent No. 5,736,137 ("Anderson patent");
   - U.S. Patent Application No. 2003/0018014A1 ("Lerner");
   - Stenbygaard *et al.*, Breast Cancer Research and Treatment 25:57-63 (1993) ("Stenbygaard"); and
   - McLaughlin *et al.*, J. Clin. Oncology, 16(8):2825-2883 (Aug. 1998) ("McLaughlin").

4. As I have previously explained, in 1998, I was a practicing physician with extensive experience treating CLL patients. I believe the opinions in my declarations are representative of the opinions that a person of ordinary skill in the art in the field of this invention would have had at that time.

5. At page 6 of the Final Action, the Examiner states that I did not provide in my earlier declaration "sufficient evidence teaching the immunotherapeutic mechanisms, host effector functions and receptor binding affinity of the CD20 antibody would differ between the two diseases, resulting in different antitumor mechanisms and significant differences in the impact of the therapy."

6. In paragraphs 20 and 29 of my earlier declaration, I explained that the CD20 antigen density on CLL cells was known to be lower than that on non-Hodgkin's lymphoma (NHL) cells, and that this unique feature of neoplastic CLL cells reduces susceptibility of these cells to cell killing by an anti-CD20 antibody.

7. Perhaps in response to these observations, the Examiner, at page 5 of the Final Action, states that the Kaminski '398 patent "plainly and clearly teaches the effectiveness of CD20 therapy for a B cell cancer and the high expression of CD20 antigen on CLL (more than 95% expression on patients with CLL)." The Examiner cites column 8, lines 9-16 of the Kaminski '398 patent to support this conclusion. The Examiner's characterization of this passage of the patent is scientifically incorrect.

8. By 1998, it was known that neoplastic B cells from CLL patients exhibit a *low density* of CD20 antigen. See, Almasri *et al.*, *Am. J. Hematol.* 40:249-263 (1992) (provided with my earlier declaration). In other words, while CD20 antigen can be detected on most neoplastic cells isolated from CLL patients, the number of antigens expressed by and accessible on the cell surface of each cell is *low* compared to other types of normal and abnormal B-cells. This low density or "dim" CD20 antigen expression was known to be a unique feature of CLL cells. See, column 1 on page 263 of Almasri *et al.*

9. By contrast, in 1998, it was known that neoplastic B-cells from patients with NHL exhibit a high density of CD20 antigen. See, for example Table 1 on page 260 of Almasri *et al.* In addition, it was believed that antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxity (CDC) were important mechanisms for the *in vivo* response of anti-CD20 antibodies in treatment of NHL patients, and that the "high-density expression" of CD20 on NHL cells was necessary for efficient lysis of neoplastic B-cells from NHL patients by CDC and ADCC mediated by anti-CD20 antibodies. See, Anderson *et al., Biochem. Soc. Trans.* 25: 705-708 at column 1 on page 706 (1997) (attached as Exhibit A).

10. The contrasting *low* level of CD20 expression on CLL cells therefore would have been one important reason why an oncologist in 1998 would have doubted that anti-CD20 antibodies could be used to effectively treat CLL patients. In particular, the low density of expression was believed to prevent anti-CD20 antibodies from mediating CDC and ADCC in neoplastic cells from CLL patients.

11. This view is reflected in later publications. For example, Farag et al. showed that the reduced levels of expression of CD20 antigen on neoplastic cells from CLL patients significantly reduces the efficacy of anti-CD20 antibodies in mediating ADCC in CLL. See, for example, Farag *et al., Blood* 103(4): 1472-1474 (2004) (attached as Exhibit B), at page 1474, column 1. Farag *et al.* explains that CDC is less likely to occur with CLL cells because those cells "often dimly express CD20". See, Farag *et al.*, page 1474, column 2. Farag *et al.* also points out that overexpression of CD55 and CD59 on B-cells prevents CDC, and that that CLL cells have been shown to overexpress these two complement inhibitors. See, Farag *et al.*, column 2 on page 1474.

12. Golay *et al.* also explains that low levels of CD20 expression reduce susceptibility of CLL cells to an anti-CD20 antibody and complement. See, Golay *et al., Blood* 98(12): 3383-3389, 3385 (2001) (attached as Exhibit C). Golay *et al.* explain that CDC was thought to be an important mechanism of action of an anti-CD20 antibody and that the degree of the lytic response (CDC activity)

depended on the level of expression of CD20 on the cells. *See,* Golay *et al.*, abstract and Fig. 8 on page 3388.

13. Therefore, even though greater than 95% of CLL patients express *some* CD20 antigen on their neoplastic cells, this would not have provided an oncologist in 1998 with a legitimate scientific basis for believing that an anti-CD20 antibody could be used to effectively treat patients with CLL. Instead, in 1998, an oncologist would have believed that the low density of expression of CD20 would have been the relevant factor, because it would render these neoplastic cells in the CLL patient not susceptible to ADCC and CDC – two mechanisms of action believed to be important to the way that anti-CD20 antibodies provided therapeutic effectiveness against neoplastic cells in NHL patients.

14. My earlier declaration also explained that another important difference between CLL and NHL was that patients with CLL have a much higher circulating tumor burden than patients with NHL. See, paragraphs 22 and 30 of my first declaration. The Examiner does not address this important difference between CLL and NHL in the Final Action.

15. The high tumor burden in CLL patients would have raised additional questions in the mind of an oncologist working in this field in 1998 about whether an anti-CD20 antibody would be effective in providing therapeutic benefits in a CLL patient. For example, an oncologist would have been concerned that a CLL patient could not mount an effective immune response against the neoplastic CLL cells in the patient following administration of the anti-CD20 antibody due to the high tumor volume.

16. Again, concerns that were held in 1998 are reflected in the scientific literature published later. For example, Kennedy *et al. J. Immunol.* 172(5): 3280-3288 (2004), copy attached as Exhibit D, identified a number of important potential issues that had been identified concerning the treatment of CLL patients with high tumor cell burdens with an anti-CD20 antibody, including: (i) that the treatment would consume so much complement that the ability of the antibody to

promote CDC could be compromised, (ii) that the capacity of the mononuclear phagocytic system (MPS) to remove IgG-opsonized cells might be exceeded at high cell counts, and (iii) that Fcγ receptor mediated rearrangement and capping of antibody-antigen complexes on the surface of B-cells might lead to removal of the complexes, thus allowing cells to escape.

17. In other words, in 1998, there were a number of significant scientific reasons why an oncologist would not have expected that an anti-CD20 antibody would provide positive clinical benefits in treating CLL patients despite the evidence of successful use of such antibodies in treating NHL patients as in the cited references.

18. The Examiner also incorrectly suggests at page 5 of the Final Action that Example IV in the Kaminski '398 patent discloses that an "unlabeled anti-CD20 antibody is used in combination with chemotherapy." The Examiner's characterization of the Kaminski '398 patent and Example IV are inaccurate.

19. The treatment methods described in the Kaminski '398 patent use monoclonal antibodies that recognize tumor-associated antigens to *deliver radioisotopes* to tumor cells (column 1, lines 46-52 of the Kaminski '398 patent). Because it was known that ß-emitters such as ^{90}Y or ^{131}I had ranges of emission resulting in a "bystander effect," cells adjacent to the cell bound by the radiolabeled antibody could be killed by the radiolabel. This is discussed at column 9, lines 23-44 of the Kaminski patent. In these methods, both the particular tumor cell antigen and the capacity or nature of binding of the antibody to it become relatively unimportant – as long as the radiolabeled antibody can bind to cells in the proximity of the tumor mass, the radioisotope bound to the radiolabeled antibody can deliver its therapeutic effect.

20. Example IV in columns 35-36 of the Kaminski '398 patent discusses "sensitization of lymphoma cells." Initially, it is important to recognize that the hypothesis described in this paragraph is not focused on CLL cells, but instead is based on the experiences of the Kaminski inventors with lymphoma cells. It also

is not supported by any experimental data, does not discuss treatment of any patient, much less a CLL patient, and provides no details about timing, dosages or other aspects of any particular possible therapeutic regimen.

21. Example IV hypothesizes that there might be synergism in the induction of apoptosis in lymphoma cells occurring as a consequence of the concurrent binding of an anti-CD20 antibody to a B-cell and the delivery to that B-cell of a dose of irradiation via the radiolabeled antibody. See, Kaminski '398 patent at column 35, lines 37-38. Based on this hypothesis, Kaminski suggests that it might be possible to achieve a similar synergism through the administration of a non-radiolabeled antibody to CD20 plus "a second antibody, directed against a different antigen than CD20, that is conjugated to a radionucleotide." As Kaminski suggests, this "would provide the same synergistic second insult to the tumor cell as is provided by an anti-CD20 radioimmunoconjugate." See, Kaminski '398 patent at column 35, lines 42 to 51. In other words, to achieve the desired effect, this process would employ an non-radiolabeled anti-CD20 antibody, which would not have an independent therapeutic effect, with a second radiolabeled antibody against a different B-cell antigen, which would irradiate the cells.

22. The Kaminski '398 patent then refers to other theoretical approaches for potentially achieving "synergism in the induction of apoptosis" in lymphoma. These approaches include external beam irradiation (column 35, lines 53-60) or administering a chemotherapeutic agent (paragraph spanning columns 35 to 36). These additional passages do not indicate that a non-radiolabeled anti-CD20 antibody should be combined with these other treatments.

23. I do not believe an oncologist would have used the information provided in this Example or elsewhere in the Kaminski patent to devise a new treatment method for CLL in 1998 using non-radiolabeled anti-CD20 antibodies. In 1998, as I have explained, an oncologist would question whether a significant ADCC or CDC response could be induced in a CLL patient by administration of a non-radiolabeled anti-CD20 antibody due to the low levels of CD20 expression by

neoplastic cells in CLL patients, and the high volume of those cells in the patient. This would have, at a minimum, raised serious questions about whether any positive clinical benefits would be seen in CLL patients given a non-radiolabeled anti-CD20 antibody. None of these issues are resolved by the information provided in Example IV or elsewhere in the Kaminski '398 patent, as the approaches described in the Kaminski patent depend on use of radiolabeled antibody that kills targeted cells using a fundamentally different mechanism.

24. Because of this, even if the Kaminski '398 patent had shown that *radiolabeled* anti-CD20 antibodies provided some positive clinical benefits in *CLL* patients (which it did not), this fact would not have led an oncologist familiar with CLL to believe that administration of *non-radiolabeled* anti-CD20 antibody would be effective in treating CLL. Instead, given the emphasis throughout the Kaminski '398 patent on *radioimmunotherapy* and the observations in the patent about the "limited efficacy of unmodified antibodies" (column 2, lines 20-22), I believe the patent actually would have taught away from the idea of treating CLL patients with non-radiolabeled anti-CD20 antibodies as required by claims 29, 55 and 97 of the '347 application.

25. At page 5 of the Final Action, the Examiner states that there "seems to be no factual evidence presented suggestive of failure of treatment of CLL in a patient." I disagree. I believe I identified a substantial amount of factual evidence in my earlier declaration that shows why an oncologist would not believe that treatment of CLL patients using an anti-CD20 antibody would be therapeutically effective based on the references cited in the Final Action. See, for example, paragraphs 6-15 and 28-33 of my earlier declaration.

26. In addition, I believe my personal experiences from 1998 are also relevant. In 1998, I became aware of the use of the anti-CD20 antibody rituximab to treat NHL. Despite this, I did not use rituximab to treat CLL patients under my care. I did not do this because I did not think that rituximab would provide positive clinical benefits given the significant differences between the diseases and the

unique characteristics of neoplastic CLL cells. I also had major concerns about serious adverse side effects related to the very high tumor cell burdens in CLL patients.

27. The publications I cited in my earlier declaration and in this declaration also provide the evidence that the Examiner has requested. These publications document the low density of CD20 expression on cells from CLL patients and the high circulating tumor burden in CLL patients, which support my opinion that oncologists would have believed in 1998 that an anti-CD20 antibody-based treatment regimen for CLL patients would not have provided positive clinical benefits to CLL patients.

28. In addition to these reasons, I believe there is additional scientific evidence in the literature showing that administration of anti-CD20 antibodies did not provide positive clinical benefits for CLL patients. In particular, I note that Jensen *et al. Ann. Hematol.* 77: 89-91 (1998) (attached as Exhibit E, and previously provided to the Examiner) presents evidence of a failed attempt to treat a CLL patient using rituximab.

29. Jensen *et al.*, reports administration of rituximab to a patient with CLL at a dose of 375mg/m^2. After administration of the first infusion of rituximab, the patient suffered "severe side effects," which the authors attribute to "rapid tumor lysis syndrome." See, Jensen *et al.*, column 1 on page 89. While three further infusions were administered "without clinical problems," the paper reports that the treatment was *ineffective* – the patient showed signs of progressive disease at 3 weeks requiring salvage chemotherapy. See, Jensen *et al.*, at page 90, column 2.

30. The serious side effect of rapid tumor cell lysis reported in Jensen *et al.* was the basis of one of the concerns I had in 1998 about administration of an anti-CD20 antibody to a patient with a high circulating tumor burden. As Jensen *et al.* point out, "physicians must be aware of this hitherto unreported phenomenon in patients with high CD20-positive blood counts." See, Jensen *et al.*, at page 89 (summary).

31. I also note that the abstract of Jensen *et al.* explains that earlier trials in follicular lymphoma excluded patients with lymphocytes > 5 x 10^9/L (such high tumor burdens being characteristic of CLL). Given the serious side effects and lack of positive clinical benefits in CLL patients as reported by Jensen *et al.*, this suggests that the decision to exclude patients with lymphocyte counts > 5 x 10^9/L in McLaughlin *et al.* was not made for the simple purpose of "streamlining the patient population for testing" as the Examiner suggests at page 4 of the Final Action. Instead, a more plausible explanation is that the authors believed that administration of anti-CD20 antibodies to CLL patients would place them at risk of serious side effects with no prospect for positive clinical benefits.

32. Jensen *et al.* also refers to minor "clinical side effects" in six additional CLL patients treated with rituximab. The paper, however, does not report that rituximab was clinically active in any of these patients. In view of the ineffectiveness in the patient that is the focus of the Jensen *et al.* report, I believe an oncologist would have concluded that the other patients given rituximab, likewise, did not achieve a positive clinical benefit from the treatment.

33. I understand that all of the pending claims of the '347 application require administration of an anti-CD20 antibody "*in an amount effective to treat the CLL*." This means to me that the treatment must result in a positive clinical benefit to the CLL patient. I do not believe a method that results in the continued progression of the CLL disease in the patient would be considered to be "effective to treat CLL" by an oncologist. In addition, a method that induces only an undesirable and life-threatening condition in the CLL patient, such as rapid tumor cell lysis, would not qualify as being a method that is "effective to treat the CLL."

34. My opinion of what this expression in the claims would convey to an oncologist is consistent with the specification of the '347 application, which refers to treatment methods that result in, for example, demonstrated efficacy with minimal infusion-related toxicity (page 8, paragraph 0320), overall response rate (ORR), complete responses (CR), partial responses (PR), improved median time to progression or

improved duration of response (page 9, paragraph 0340 as well as page 14, paragraph 0440), or remission upon treatment (page 11, paragraph 0370).

35. The treatment of CLL patients using anti-CD20 antibodies is an important medical advance addressing a long felt need in the treatment of CLL. CLL is the most common form of leukemia in adults, has an incidence of approximately 15,000 cases per year in the United States, and annually causes about 4,500 deaths. In 1998, the clinical prognosis for an individual with CLL was bleak, and that outcome in the treatment of CLL had improved little over the preceding 30 years. See, Catovsky *et al. European Journal of Cancer* 31A Nos. 13/14: 2146-2154 (1995) (copy attached as Exhibit F).

36. The treatment regimes described and claimed in the '347 application are effective in treating CLL, in both previously untreated CLL patients (see, for example, Halleck *et al., Blood* 112(11), Abstract 325 (2008), copy attached as Exhibit G) and in CLL patients in which chemotherapy has failed to slow the progression of the disease (see, for example, Robak *et al. Blood* 112(11): Abstract LBA-1 (2008), copy attached as Exhibit H). Halleck *et al.* and Robak *et al.* report phase III clinical trials confirming that CLL can be treated in human patients by administering an anti-CD20 antibody to the patients in an amount effective to treat the CLL as disclosed and claimed in the '347 application. Complete responses, partial responses, and improved median progression-free survival confirm the therapeutic efficacy of this treatment regimen. The trials did not include treatment with a radiolabeled antibody or use of radiation in conjunction with the therapeutic anti-CD20 antibody. The data from these trials demonstrates the effectiveness of the claimed methods of treating CLL patients, and establishes that the claimed treatment methods address the long felt need for a safe and effective way to treat CLL patients.

37. In addition, at the time of the invention, the most viable method of treatment of CLL patients was using fludarabine. See Catovsky *et al.* While fludarabine is useful in treating many patients, there are a significant number of patients who

do not respond to fludarabine. These fludarabine-refractory patients had no viable alternative treatment options in 1998. Again, the treatment method being claimed in the '347 application responds to the long felt need for a viable way to treat these CLL patients.

38. The CLL treatment methods disclosed and claimed in the '347 application was approved the European Medicines Agency (EMEA) earlier this year, and is expected to obtain marketing approval by the Food and Drug Administration (FDA) later this year. CLL treatment with an anti-CD20 antibody is considered by hematology oncologists to be a significant medical breakthrough that will "change practice." See, for example: www.roche.com/media/media_releases/med-cor-2009-02-27.htm, and www.medpagetoday.com/MeetingCoverage/ASHHematology/12054, copies attached as Exhibits I and J, respectively. In my opinion, the methods of CLL treatment in the '347 application will become the standard of care for CLL patients in the future.

* * *

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of any patent granted on this application.

David P. Schenkein, M.D.

Date: 05/05/09